

Mixed molecular motor traffic on nucleic acid tracks: models of transcriptional interference and regulation of gene expression*

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RNA polymerase (RNAP) is molecular machine that polymerizes a RNA molecule, a linear heteropolymer, using a single stranded DNA (ssDNA) as the corresponding template; the sequence of monomers of the RNA is dictated by that of monomers on the ssDNA template. While polymerizing a RNA, the RNAP walks step-by-step on the ssDNA template in a specific direction. Thus, a RNAP can be regarded also as a molecular motor and the sites of start and stop of its walk on the DNA mark the two ends of the genetic message that it transcribes into RNA. Interference of transcription of two overlapping genes is believed to regulate the levels of their expression, i.e., the overall rate of the corresponding RNA synthesis, through suppressive effect of one on the other. Here we model this process as a mixed traffic of two groups of RNAP motors that are characterized by two distinct pairs of start and stop sites. Each group polymerizes identical copies of a RNA while the RNAs polymerized by the two groups are different. These models, which may also be viewed as two interfering totally asymmetric simple exclusion processes, account for all modes of transcriptional interference in spite of their extreme simplicity. A combination of mean-field theory and computer simulation of these models demonstrate the physical origin of the switch-like regulation of the two interfering genes in both co-directional and contra-directional traffic of the two groups of RNAP motors.

I. INTRODUCTION

Synthesis of messenger RNA, a linear heteropolymer, using the corresponding template DNA, is called transcription; it is carried out by a molecular machine called RNA polymerase (RNAP) [1]. This machine also exploits the DNA template as a filamentous track for its motor-like movement consuming input chemical energy [2]. Polymerization of each RNA by a RNAP takes place in three stages: (a) initiation at a specific ‘start’ site (also called initiation site) on the template, (b) step-by-step elongation of the RNA, by one nucleotide in each forward step of the RNAP motor, and (c) termination at a specific ‘stop’ site (also called termination site) on the template. For the sake of convenience, throughout this paper we refer to the segment of the template DNA between the start and the stop sites as a ‘gene’.

RNAPs moves from 3′ to the 5′ direction on a single strand of DNA. Often multiple RNAPs polymerize the same gene simultaneously. In such RNAP traffic [3, 4], all the RNAPs engaged simultaneously in the transcription process move in the same direction while polymerizing identical copies of a RNA, all by initiating transcription from the same start site and terminating at the same stop site. Since any segment of the template DNA covered by one RNAP is not accessible simultaneously to any other RNAP, this steric exclusion gives rise to nontrivial spatio-temporal organization of RNAPs in RNAP traffic. Theoretical models of this kinetic process have been developed over the last few years [4, 5, 24–27] by appro-

priately adapting, and extending, asymmetric exclusion process (ASEP) [6, 7], a popular model in nonequilibrium statistical mechanics that we describe briefly in the next section

In this communication we report theoretical studies of more complex RNAP-traffic phenomena that are believed to play important regulatory roles in living cells [8–11]. These phenomena arise from simultaneous transcription of two overlapping genes either on the same DNA template or two genes on the two adjacent single strands of a duplex (double-stranded) DNA. In the former case, traffic is entirely uni-directional although RNAPs transcribing different genes polymerize two distinct species of RNA molecules by starting (and stopping) at different sites on the same template DNA strand. In contrast, in the latter case, RNAP traffic in the two adjacent “lanes” move in opposite directions transcribing the respective distinct genes. In both these situations the phenomenon of suppressive influence of one transcriptional process on the other is called transcriptional interference (TI) [12, 13].

In general, a RNAP at the initiation, elongation or termination stage of one transcriptional process can suppress the initiation, or elongation (or termination) of the other transcription by another RNAP [8–10]. In other words, the stages of transcription of the two interfering RNAPs define a distinct mode of interference. Different modes of interference have been assigned different names like “occlusion”, “collision”, “sitting duck interference”, etc. [12]. Many pairs of interfering transcription processes are known to form a bistable switch: switching ON a high level of transcription of one of the two genes can switch OFF the other by its suppressive effect [8–10]. The main aim of this communication is to demonstrate this effect using a unified theoretical framework that we

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develop here. This framework is capable of throwing light on many other kinetic aspects of TI phenomena.

In this paper we develop a unified theoretical framework that, for a given relative orientation of two genes, captures all possible modes of TI by a single set of master equations. Solving these equations, we investigate the effects of TI on the rates of the two transcriptions. Moreover, by carrying out extensive computer simulations of our model, we also test the validity of the mean-field approximations made in formulating the master equations. We explore the effects of the spatial extent and relative orientation of the overlap of the two genes as well as those of the kinetic parameters like initiation rates. Our results demonstrate interesting regulatory phenomena arising from TI. In particular, the transcription of one gene can be practically switched off by increasing that of another to a sufficiently high level.

II. MODEL

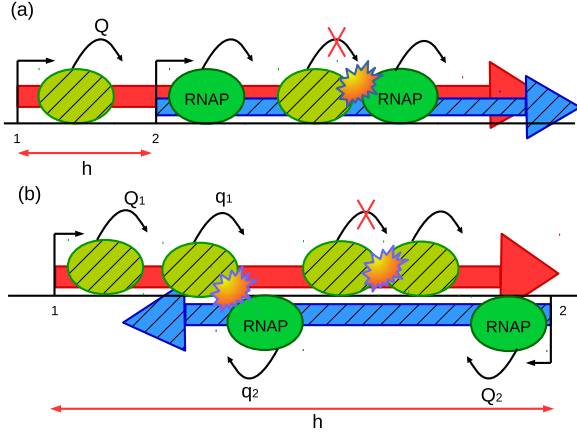


FIG. 1: Schematic representation of TI model. (a) Codirectional mixed traffic with separate ramps: transcription of two overlapping genes. (b) Contradirectional traffic on adjoining unequal tracks: sense and anti-sense transcription of two overlapping genes

We represent a single-stranded DNA (ssDNA) by a linear chain (i.e., a one-dimensional lattice) of equispaced sites that are labelled by the integer index i . Each site of this lattice denotes a nucleotide which is a monomeric subunit of the DNA track. The chain serves both as the template and track for the respective RNAP motors that are engaged in its transcription. We also represent each RNAP by a hard rod, i.e., an extended particle, of length ℓ in the units of nucleotide length, i.e., it covers ℓ successive sites of the lattice simultaneously. Normally, ℓ is typically 30 to 35 nucleotides. We denote the position of a RNAP on its track by the lattice site at which the *left-most* unit of the rod is located while the next $\ell - 1$ sites of the lattice are merely *covered* by the RNAP. Thus, if the lattice site j denotes the position of a RNAP then the

RNAP covers not only the site j but also the next $\ell - 1$ sites $j + 1, j + 2, \dots, j + \ell - 1$. The RNAPs interact with each other with only hard core repulsion that is captured by imposing the condition that no lattice site is allowed to be covered by more than one RNAP simultaneously.

We model both codirectional TI (TTI) and contradirectional TI (CTI) using suitably extended TASEPs. For modeling interference of the expression of two genes we incorporate two interfering TASEPs each characterized by the respective distinct pair of start and stop sites and two distinct species of RNAP motors. For modeling TTI only a ssDNA template needs to be treated as the track for both group of RNAP motors that transcribe the two distinct genes simultaneously. But, for modeling simultaneous polymerization of sense and anti-sense transcripts, which are encoded on the two distinct strands of a duplex DNA, we use two antiparallel lattices on which the contra-directional traffic of the two groups of motors take place.

We identify two sites separated by h nucleotides as the start sites for the two genes; h is an integer that can be positive, negative or zero (see fig.1). A fresh initiation of transcription of a gene, however, is not possible as long as the first ℓ sites, starting from the start site of that gene, remain fully or partly covered by any other RNAP, irrespective of the identity of the gene that is being transcribed by the latter. We denote the rates of initiation of transcription of the two genes by α_1, α_2 , respectively. Whenever ℓ successive sites, starting from the start site of a gene on the DNA template is vacant, a fresh RNAP is allowed to cover those ℓ sites thereby initiating the corresponding transcription. Each RNAP carries a unique label 1 or 2 depending on which of the two genes it is engaged in transcribing; the label is assigned to it depending on the start site from where it begins its walk on its track. Irrespective of the actual numerical value of ℓ , each RNAP can move forward by only one site in each step, provided the target site is not already covered by any other RNAP. Single-site stepping rule is motivated by the fact that a RNAP must transcribe the successive nucleotides one by one. A RNAP engaged in the transcription of one of the two genes can detach from the lattice only after it reaches the stop site of the corresponding gene. However, so far as the rates of termination are concerned, we assume the corresponding rates to be $\beta_1 = \beta_2 = \beta$. $L1$ and $L2$ denote the lengths of the two genes, measured in terms of the number of lattice sites from the start to the stop sites of the corresponding gene. The interference between the transcription of these two genes takes place in the region of their overlap.

In the case of TTI no RNAP can pass the other immediately in front of it irrespective of which genes are being transcribed by the two RNAPs. This is motivated by the fact that in case of TTI both the genes are encoded on the same ssDNA strand. In contrast, in the case of CTI, when two RNAPs labelled by two distinct integer indices 1 and 2 (i.e., transcribing different genes) face each other head-on, these are allowed to pass, albeit with a hop-

ping rate that is lower than that in the absence of the obstruction, i.e., $q_1 < Q_1$ and $q_2 < Q_2$. This prescription is motivated by the fact that the genes for the sense and antisense transcripts are encoded on the two distinct complementary strands of the duplex DNA which serve as the tracks for the corresponding oppositely moving RNAP traffic. However, in the same model of CTI if a RNAP finds itself just behind another co-directional RNAP in front (i.e., both transcribe the same gene and, therefore, carry the same integer label) then the trailing RNAP remains stalled till the site in front of it is vacated by the leading RNAP. The motivation for this prescription is that the two RNAPs engaged in transcribing the same gene move on the same ssDNA strand.

A. Master equations under mean-field approximation

Let $P_\mu(i, t)$ denote the probability that at time t there is a RNAP at site i engaged in the transcription of the gene μ ($\mu = 1, 2$ for the genes 1 and 2, respectively). Note that the probability that the site i is occupied by a RNAP, irrespective of the gene it is transcribing, is given by $P(i) = \sum_{\mu=1}^2 P_\mu(i)$.

1. Co-directional traffic

Let $P(\underline{i}|j)$ be the conditional probability that, given a RNAP at site i , there is another RNAP at site j located downstream along the lattice. Obviously, $\xi(\underline{i}|j) = 1 - P(\underline{i}|j)$ is the conditional probability that, given a RNAP at site i , site j is empty. Therefore, by definition,

$$\xi(\underline{i}|i + \ell) = \frac{1 - \sum_{s=1}^{\ell} P(i + s)}{1 - \sum_{s=1}^{\ell} P(i + s) + P(i + \ell)}$$

Let $\xi(j)$ be the probability that site j is not covered by any RNAP, irrespective of the state of occupation of any other site, is given by $1 - \sum_{s=0}^{\ell-1} P(j - s)$. Note that, if site i is given to be occupied by one RNAP, the site $i - 1$ can be covered by another RNAP if, and only if, the site $i - \ell$ is also occupied.

Under mean-field approximation, the master equations governing the stochastic kinetics of the two interfering transcriptional processes are given by (for $h > 0$)

$$\begin{aligned} \frac{dP_1(1, t)}{dt} &= \alpha_1 \left(1 - \sum_{s=1}^{\ell} P(s) \right) - QP_1(1, t) \xi(\underline{1}|1 + \ell), \\ \frac{dP_1(i, t)}{dt} &= QP_1(i - 1, t) \xi(\underline{i-1}|i - 1 + \ell) - QP_1(i, t) \xi(\underline{i}|i + \ell) \quad \text{for } (1 < i < L1), \\ \frac{dP_1(L1, t)}{dt} &= QP_1(L1 - 1, t) \xi(\underline{L1-1}|L1 - 1 + \ell) - \beta P_1(L1, t), \\ \frac{dP_2(1 + h, t)}{dt} &= \underbrace{\alpha_2 \left(1 - \sum_{s=0}^{\ell-1} P_1(h - s) \right)}_{=1 \text{ for } (h=0)} \left(1 - \sum_{s=1}^{\ell} P(h + s) \right) - QP_2(1 + h, t) \xi(\underline{1+h}|1 + h + \ell), \\ \frac{dP_2(i, t)}{dt} &= QP_2(i - 1, t) \xi(\underline{i-1}|i - 1 + \ell) - QP_2(i, t) \xi(\underline{i}|i + \ell) \quad \text{for } (1 + h < i < h + L2), \\ \frac{dP_2(h + L2, t)}{dt} &= QP_2(h + L2 - 1, t) \xi(\underline{h+L2-1}|h + L2 - 1 + \ell) - \beta P_2(h + L2, t). \end{aligned} \tag{1}$$

Equations for $h < 0$ can be obtained from (1) by interchanging index 1 and 2.

2. Contra-directional traffic

Effect of CTI on gene expression can be studied by writing down and solving master equation for $P_\mu(i, t)$, which denotes the probability of finding an RNAP on

gene μ ($\mu \equiv 1, 2$) at time t , at lattice site i . Obviously, $\xi_1(\underline{i}|i + \ell)$ is the conditional probability that, given a RNAP on gene 1 at site i , site $i + \ell$ is empty. Therefore, by definition,

$$\xi_1(\underline{i}|i+\ell) = \frac{1 - \sum_{s=1}^{\ell} P_1(i+s)}{1 - \sum_{s=1}^{\ell} P_1(i+s) + P_1(i+\ell)}$$

Similarly, $\xi_2(i-\ell|\underline{i})$ is the conditional probability that, given a RNAP on gene 2 at site i , site $i-\ell$ is empty. Therefore, by definition,

$$\xi_2(i-\ell|\underline{i}) = \frac{1 - \sum_{s=1}^{\ell} P_2(i-s)}{1 - \sum_{s=1}^{\ell} P_2(i-s) + P_2(i-\ell)}$$

Let $\xi_1(j)$ be the probability that site j on gene 1 is not covered by any RNAP, irrespective of the state of occupation of any other site. obviously, $\xi_1(j) = 1 - \sum_{s=0}^{\ell-1} P_1(j-s)$. Similarly, $\xi_2(j)$, the probability that site j on gene 2 is not covered by any RNAP, irrespective of the state of occupation of any other site, is given by $1 - \sum_{s=0}^{\ell-1} P_2(j-s)$.

Under mean-field approximation, the master equations are written as

$$\begin{aligned} \frac{dP_1(1,t)}{dt} &= \alpha_1 \left[1 - \sum_{s=1}^{\ell} P_1(s,t) \right] \underbrace{\left[1 - \sum_{s=1}^{\ell} P_2(s,t) \right]}_{=1 \text{ for } (h-L2>\ell)} - P_1(1,t)\xi_1(\underline{1}|1+\ell) [Q_1\xi_2(1+\ell) + q_1\{1 - \xi_2(1+\ell)\}], \\ \frac{dP_1(i,t)}{dt} &= P_1(i-1,t)\xi_1(\underline{i-1}|i-1+\ell) [Q_1\xi_2(i-1+\ell) + q_1\{1 - \xi_2(i-1+\ell)\}] \\ &\quad - P_1(i,t)\xi_1(\underline{i}|i+\ell) [Q_1\xi_2(i+\ell) + q_1\{1 - \xi_2(i+\ell)\}] \quad \text{for } , (1 < i < L1) , \\ \frac{dP_1(L1,t)}{dt} &= P_1(L1-1,t)\xi_1(\underline{L1-1}|L1-1+\ell) [Q_1\xi_2(L1-1+\ell) + q_1\{1 - \xi_2(L1-1+\ell)\}] - \beta P_1(L1,t), \\ \frac{dP_2(1+h,t)}{dt} &= \alpha_2 \underbrace{\left[1 - \sum_{s=0}^{\ell-1} P_1(1+h-s,t) \right]}_{=1 \text{ for } (h-L1>\ell)} \left[1 - \sum_{s=0}^{\ell-1} P_2(1+h-s,t) \right] \\ &\quad - P_2(1+h,t)\xi_2(1+h-\ell|\underline{1+h}) [Q_2\xi_1(h) + q_2\{1 - \xi_1(h)\}], \\ \frac{dP_2(i,t)}{dt} &= P_2(i+1,t)\xi_2(i+1-\ell|\underline{i+1}) [Q_2\xi_1(i) + q_2\{1 - \xi_1(i)\}] \\ &\quad - P_2(i,t)\xi_2(i-\ell|\underline{i}) [Q_2\xi_1(i-1) + q_2\{1 - \xi_1(i-1)\}] \quad \text{for } , (2+h-L2 < i < 1+h) , \\ \frac{dP_2(2+h-L2,t)}{dt} &= P_2(3+h-L2,t)\xi_2(3+h-L2-\ell|\underline{3+h-L2}) [Q_2\xi_1(2+h-L2) + q_2\{1 - \xi_1(2+h-L2)\}] \\ &\quad - \beta P_2(2+h-L2,t). \end{aligned} \tag{2}$$

III. RESULTS

Solving the master equations (1) and (2) numerically under steady state conditions we obtained the corresponding rates of the transcriptions of the two genes. Moreover, in order to test the range of validity of the MFA made in writing the master equations, we also carried out extensive direct computer simulations of our model using the same set of parameter values that we used for solving the master equations. During the simulations, we monitored the flux of the RNAPs. The system needed, typically, about two million time steps to attain

the steady state after which we collected the steady-state data over the next five million time steps. The steady-state properties presented in this paper are averages of the data collected only in the steady state of the system. All the numerical results plotted in this paper have been obtained for $\ell = 10$, $L_1 = 1000$ and $L_2 = 1100$; by comparing with the results for a few other lengths of RNAPs and genes, we ensured that our conclusions do not suffer from any artefacts of the choice of these parameters.

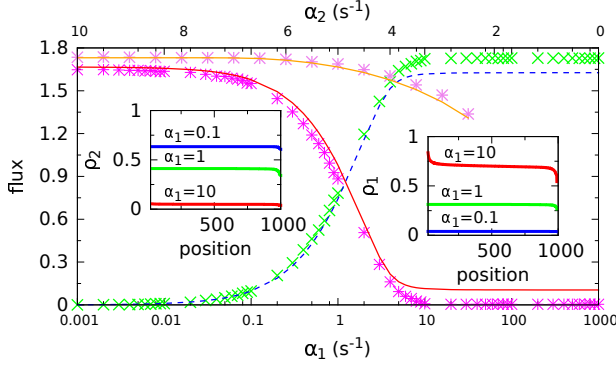


FIG. 2: Codirectional: The switch like behavior of fluxes of RNAPs, plotted as a function of α_1 , for $Q = 30 \text{ s}^{-1}$, $\alpha_2 = 5 \text{ s}^{-1}$, $\beta_1 = \beta_2 = 1000 \text{ s}^{-1}$ and $h = 20 \text{ bp}$. The dashed line and solid line corresponds to our mean-field theoretic predictions for flux 1 and flux 2 respectively whereas the discrete data points (cross and star corresponds for flux 1 and flux 2 respectively) have been obtained from computer simulations. The insets show the average density profiles for three different values of α_1 . When the gene does not have a transcriptional interference, its expression follows different kinetics. Corresponding flux is plotted as a function of α_2 , for $Q = 30 \text{ s}^{-1}$ ($\alpha_1 = 0$). The solid orange line corresponds to our mean-field theoretic predictions and violet data points have been obtained from computer simulations.

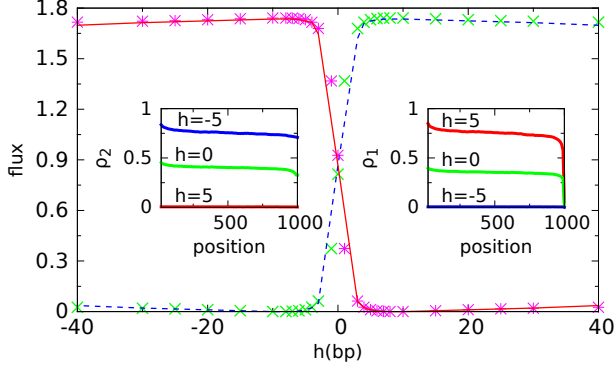


FIG. 3: Codirectional: The roles of the two genes as “suppressor” and “suppressed” are interchanged as h is varied from $-N$ to $+N$ ($N=40$ in this figure just for illustration).

A. Results for co-directional traffic

In fig.2 we plot the fluxes of RNAPs in the two traffic which, as explained above, are the overall rates of transcription of the two genes. First of all, note that for any given value of α_2 , gene 2 would have got transcribed normally at a fairly high rate if the gene 1 were not interfering with its transcription. As long as α_1 is not too high, the rate of transcription of gene 2 is weakly affected by infrequent co-directional “collisions” and proceeds at a fairly high rate. But, as α_1 increases the time

gap detected at any arbitrary site between the departure of a RNAP and the arrival of the next RNAP becomes shorter. Therefore, the site for the initiation of transcription of gene 2, which is located on the path of the RNAP traffic on gene 1, remains “occluded” for most of the time if α_1 is sufficiently high. Consequently, a high rate of expression of gene 1 strongly suppresses the expression of gene 2, irrespective of the actual numerical value of α_2 . Thus, the rates of transcription of the two genes are strongly anti-correlated.

The role of “suppressor” and suppressed” genes are interchanged as the separation h between the transcription initiation sites is varied from a positive integer to a negative integer (see fig.3) The sharp changes take place only over a narrow interval of the order of ℓ around $h = 0$.

B. Results for contradirectional traffic

Although the results on flux, plotted in fig.4, are qualitatively similar to the corresponding results for co-directional traffic plotted in fig.2, there are some additional features. The kinks observed in the density profiles shown in the insets of fig.4 are consequences of the extended “defect” created by the slower moving RNAPs against the faster moving ones [14].

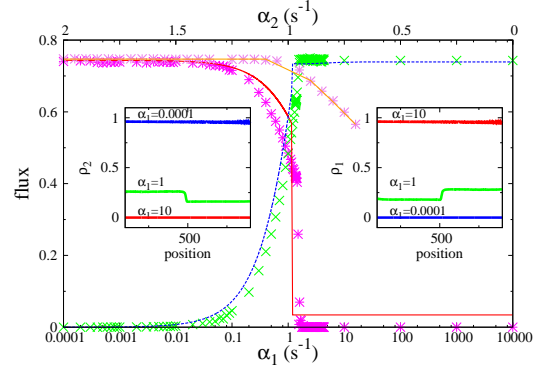


FIG. 4: Contradirectional: Same as in fig.2, except that the traffic is contradirectional and $h = 500$, $Q_1 = Q_2 = 30 \text{ s}^{-1}$, $q_1 = q_2 = 10 \text{ s}^{-1}$, $\alpha_2 = 1.0 \text{ s}^{-1}$, $\beta_1 = \beta_2 = 1.0 \text{ s}^{-1}$, $L_1 = L_2 = 1000$.

IV. SUMMARY AND CONCLUSION

Co-directional and contra-directional two-species TASEP, both on a single track and two parallel tracks, have been studied earlier for purely theoretical consideration as well as for capturing real physical processes [15–18]. But, in all those models a single pair of start and stop sites serve as the entry and exit points for both species of particles. Motivated by cytoskeletal motor traffic, TASEP-based models with two distinct species of oppositely moving self-propelled particles have been

developed earlier [19–23]. Since those motors can attach to and detach from any lattice site, except for quantitative difference in the values of attachment/detachment, the motor kinetics at the two ends of the track were qualitatively no different from those at any other site. In contrast, for the transcription of a specific gene, RNAP motors have to start and stop their walk at pre-designated sites. Moreover, premature detachment of a RNAP, which would produce a truncated RNA strand, is not allowed in our model because such errors occur very rarely.

In most of the earlier theoretical models on RNAP traffic [24–28] all the RNAP were engaged in transcribing a single gene; therefore the traffic was uni-directional and every RNAP polymerized identical copies of the RNA while a single pair of start-stop sites marked the points of initiation and termination of transcription. In contrast, in the models reported in this paper two distinct pairs of start-stop sites mark the points of initiation and termination of the respective genes. Moreover, the RNA species that gets polymerized by a RNAP depends on the sites from which it initiates transcription. Thus copies of two distinct species of RNA get synthesized simultaneously by a mixed population of two groups of RNAP motors the relative direction of whose movements is dictated by the relative orientation of the two genes.

In our model of TI in co-directional mixed RNAP traffic we assumed that a RNAP passively waits at its current position if the target nucleotide in front is already cov-

ered by another RNAP. The temporarily stalled RNAP can resume its forward movement, and the concomitant transcriptional activity, only after its target site is vacated by the RNAP immediately in front of it. We have also ignored the possibility of backtracking of the individual RNAP motors [27, 29, 30]. In future extensions of our model [31], we intend to explore the effects of backtracking, active re-starting of stalled RNAP by a trailing RNAP [32, 33] as well as premature detachment of RNAPs upon suffering collision.

In addition to the differences in the models developed here and all other TASEP-type models described above, the main questions addressed in those models are also fundamentally different from those addressed in this paper. In all the earlier theoretical works the effects of the different modes of interference have been studied separately [34, 35]. The simple TASEP-based unified model that we have developed here not only captures all possible modes of transcriptional interference, but also accounts for the self-regulation of the pair of genes through the adaptation of the levels of their interfering transcriptions.

Acknowledgements

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